PERSPECTIVES

Brain glucose and lactate uptake during exhaustive exercise

Niels H. Secher[1] and Bjørn Quistorff[2]
[1]*The Copenhagen Muscle Research Centre, Department of Anaesthesia, Rigshospitalet*
Email: nhsecher@rh.dk
[2]*Department of Biochemistry and Genetics, The Panum Institute, University of Copenhagen, Denmark*
Email: bq@imbg.ku.dk

With the introduction of the Kety-Schmidt method in 1945, cerebral blood flow (CBF) and its metabolic rate for oxygen ($CMRO_2$) were determined and both were found to remain remarkably stable with only small reductions during sleep. An experimental evaluation of the complex function of the brain had to wait a decade. The use of radioactive tracers by Lassen and Munck allowed the regional values (rCBF and $rCMRO_2$) to be determined. Thus during cerebral activation, $rCMRO_2$, and even more so rCBF, increase in relevant areas of the brain. This finding is so consistent that cerebral activation has become synonymous with enhanced $rCMRO_2$ and rCBF values as detected by e.g. positron emission tomography (PET).

However, the energy metabolism of the activated brain seems more complex than enhanced $rCMRO_2$, and thereby rCBF. Normally, the brain is considered to rely on glucose as its substrate for aerobic metabolism and thus the ratio between its uptake of oxygen and glucose is close to 6. Yet that does not hold for the activated brain. Using PET, Fox *et al.* (1988) found the regional cerebral metabolic ratio for the activated brain to decrease in response to visual stimulation and a globally decreased ratio was confirmed by determination of the arterio-venous difference for oxygen and glucose (Madsen *et al.* 1995). Subsequently it was observed that the brain activation associated with intense exercise also decreases the metabolic ratio (Ide *et al.* 2000). Compared to other means of activating the brain, intense exercise is unique in the sense that it is associated with a high blood lactate and the brain takes up lactate from the blood in proportion to its arterial concentration to make the cerebral metabolic ratio ($CMRO_2$/glucose + $^1/_2$lactate) decrease to its lowest level of ~3 at exhaustion following 4-limb exercise (Dalsgaard *et al.* 2004*a*). This transient deviation of the metabolic ratio from 6 may be calculated to correspond to a 'surplus' carbohydrate uptake in the brain of up to 10 mmol, i.e. it can reach the magnitude of the brain glycogen level.

The work by Kemppainen *et al.* (2005) (this issue of *The Journal of Physiology*) makes a significant contribution to the puzzle of understanding the metabolism of the activated brain. It demonstrates, although indirectly, that lactate taken up by the brain following exercise decreases the glucose uptake suggesting that the neurones prefer lactate for acute acceleration of their metabolism. Kemppainen *et al.* (2005) take advantage of the fact that blood lactate reaches its highest level in the first minutes after intense exercise which coincides with the time when the cerebral metabolic ratio reaches its nadir (Ide *et al.* 2000; Dalsgaard *et al.* 2004*a*). It is not possible to perform maximal exercise in a PET scanner, but by making the evaluation of the brain's uptake of glucose right after exercise, a PET evaluation becomes feasible. They find that following ergometer cycling there is a decreased glucose metabolism in all regions of the brain. This appears to be at variance with the arterio-venous difference data on the glucose balance across the brain which shows an increased uptake (Madsen *et al.* 1995; Ide *et al.* 2000; Dalsgaard *et al.* 2004*a*). However, the fact that Kemppainen *et al.* study the details of a 90 min recovery phase after exercise, while the previous studies have focused on the events directly related to the activation, may be part of the explanation.

The decreasing metabolic ratio for the activated brain remains unexplained and the lactate uptake by the brain during and after exercise makes an understanding of brain metabolism even more complicated. The change of the ratio during intense activation probably involves glycogen metabolism, although concomitant measurements of the glycogen level are not available. With aerobic metabolism the effect of glycogen breakdown on the ratio, if any, would be an increase rather than a decrease, since glucose is spared corresponding to the amount of glycogen broken down. On the other hand a decreased ratio, corresponding to the surplus in glucose uptake relative to oxygen, would occur if brain activation is associated with significant anaerobic metabolism. This would, however, result in lactate accumulation and subsequently lactate export from the brain during activation which is not observed, at least within the first hour of recovery (Dalsgaard *et al.* 2004*b*). We have preliminary data demonstrating an increased ratio during anaesthesia (typically to 6.6), although sleep would be expected to be associated with a build-up of glycogen. An alternative possibility is that the carbohydrate taken up by the activated brain is used for the formation of amino acids. As evaluated by the concomitant uptake of ammonium, the generation of amino acids could account for ~10% of the 'extra' carbohydrate taken up by the activated brain (Nybo *et al.* 2005).

The study by Kemppainen *et al.* provokes speculation as to the fate of the carbohydrate taken up by the brain. We now think that lactate taken up by the activated brain is metabolized as it does not accumulate within the brain or in the spinal fluid (Dalsgaard *et al.* 2004*b*) and it is known to be a substitute for glucose metabolism (Magistretti *et al.* 1999). We need to know what happens to the enhanced glucose and lactate uptake. A suggestion is to evaluate the cerebral glucose and lactate metabolism by stable isotopes to elucidate the fate of the carbohydrate carbon during and after exercise. Ideally such evaluation should be carried out together with a PET evaluation of the glucose uptake on a regional level as carried out by Kemppainen *et al.*

Dalsgaard MK *et al.* (2004*a*). *Am J Physiol Regul Integr Comp Physiol* **287**, R534–R540.
Dalsgaard MK *et al.* (2004*b*). *J Physiol* **554**, 571–578.
Fox PT *et al.* (1988). *Science* **241**, 462–464.
Ide K *et al.* (2000). *J Physiol* **522**, 159–164.
Kemppainen J *et al.* (2005). *J Physiol* **568**, 323–332.
Madsen PL *et al.* (1995). *J Cereb Blood Flow Metab* **15**, 485–491.
Magistretti PJ *et al.* (1999). *Science* **283**, 496–497.
Nybo L *et al.* (2005). *J Physiol* **563**, 285–290.

 DOI: 10.1113/jphysiol.2005.095786